FORM PTO-1390 (REV. 9-2001) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
P/42-63	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	
10/009380	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE
PCT/EP00/06061	29 June 2000
PRIORITY DATE CLAIMED	
30 June 1999	

TITLE OF INVENTION: GRF-CONTAINING LYOPHILIZED PHARMACEUTICAL COMPOSITIONS

APPLICANT(S) FOR DO/EO/US: Fabrizio Samaritani, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [ ] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [x] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [x] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [x] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). Unsigned
10. [x] ~~An English language translation of the annexes~~ of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [x] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [x] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordan
18. [ ] A second copy of the published international application und
19. [ ] A second copy of the English language translation of the inte
20. [x] Other items or information:
    Print EFS Sheet
    Return Postcard

EXPRESS MAIL CERTIFICATE

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office Addressee (Mail Label EL 924390251 US) in an envelope addressed to: U.S. Patent and Trademark Office, PO Box 2327, Arlington, VA 22202, on December 3, 2001

Tamika Sumpter
Name of Person Mailing correspondence

Tamika Sumpter
Signature

December 3, 2001
Date of Signature

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/009380	PCT/EP00/06061	P/42-63

21. [x] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	10 - 20 =		x **$18.00**	$	
Independent claims	1 - 3 =		x **$84.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$	
SUBTOTAL =				$	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$890.00	
				Amount to be refunded:	$
				charged:	$

a. [x] A check in the amount of $890.00 to cover the above fees is enclosed. **Check No.** _____

b. [ ] Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [x] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0700**. A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

OSTROLENK, FABER, GERB & SOFFEN, LLP
1180 Avenue of the Americas
New York, NY 10036-8403

Tel: (212) 382 0700

Edward A Meilman
SIGNATURE

Edward A. Meilman
NAME

24,735
REGISTRATION NUMBER

P/42-63

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Fabrizio Samaritani

Serial No.: Not Yet Assigned

Intl. Filing Date: June 29, 2000

Date: December 3, 2001

Group Art Unit:

Examiner: Not Yet Assigned

For: GRF-CONTAINING LYOPHILIZED PHARMACEUTICAL COMPOSITIONS

Asst. Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination please amend the application as follow.

FEE CALCULATION

In the event the actual fee is greater than the payment submitted or is inadvertently not enclosed or if any additional fee during the prosecution of this application is not paid, the Patent Office is authorized to charge the underpayment to Deposit Account No. 15-0700.

CONTINGENT EXTENSION REQUEST

If this communication is filed after the shortened statutory time period had elapsed and no separate Petition is enclosed, the Commissioner of Patents and Trademarks is petitioned, under 37 C.F.R. § 1.136(a), to extend the time for filing a response to the outstanding Office Action by the number of months which will avoid abandonment under 37 C.F.R. § 1.135. The fee under 37 C.F.R. § 1.17 should be charged to our Deposit Account No. 15-0700.

AMENDMENTS

_✓_ If checked, amendment(s) to the specification and/or claims are submitted herewith.

1. _✓_ If checked, an abstract is submitted as the last page of Appendix A.

2. Claims:

Please amend claims 3-9 pursuant to 37 C.F.R. § 1.121(c)(i) as set forth in the "clean" version attached hereto as Appendix A. Entry is respectfully requested. A version with markings to show the changes made pursuant to 37 C.F.R. § 1.121(c)(ii) is attached hereto as Appendix B.

REMARKS/ARGUMENT

The Preliminary Amendment is being submitted to change the multiple dependent claims to single dependent claims in order to eliminate the improper multiple dependent claims and to reduce the government filing fee.

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office Addressee (Mail Label EL924390251US)in an envelope addressed to: U.S. Patent and Trademark Office, PO Box 2327, Arlington, VA 22202 on December 3, 2001

Tamika Sumpter
Name of person mailing correspondence

Tamika Sumpter
Signature

December 3, 2001
Date of Signature

Respectfully submitted,

Edward A. Meilman
Registration No.: 24,735
OSTROLENK, FABER, GERB & SOFFEN, LLP
1180 Avenue of the Americas
New York, New York 10036-8403
Telephone: (212) 382-0700

EAM:sam

ABSTRACT

Human Growth Hormone Releasing Factor (GRF)- containing pharmaceutical compositions are described, more precisely, lyophilized compositions of hGRF stabilized by means of saccharose.

APPENDIX A

"CLEAN" VERSION OF EACH PARAGRAPH/SECTION/CLAIM
37 C.F.R. § 1.121(b)(ii) AND (c)(i)

CLAIMS (with indication of amended or new):

(Amended) 3. The pharmaceutical composition according to claim 1, wherein the stabilizing agent is saccharose alone.

(Amended) 4. The pharmaceutical composition according to claim 1, containing 3 or 10 mg/vial of hGRF.

(Amended) 5. The pharmaceutical composition according to claim 1 comprising 3 or 10 mg/vial of hGRF and 20.52 or 68.4 mg/vial of saccharose.

(Amended) 6. The pharmaceutical composition according to claim 1 further comprising buffering agents.

(Amended) 7. A process for preparing a pharmaceutical composition according to claim 1, comprising the preparation of an aqueous solution of the components, the distribution within containers and the lyophilization in the containers.

(Amended) 8. Forms of presentation of said pharmaceutical composition comprising the solid mixture according to claim 1, hermetically closed in a sterile condition within a container suited for storage before use and for reconstitution of the mixture into a solvent or into a solution for injectables.

(Amended) 9. A solution comprising the solid mixture according to claim 1, reconstituted in a solvent or a solution for injectables.

APPENDIX B

VERSION WITH MARKINGS TO SHOW CHANGES MADE
37 C.F.R. § 1.121(b)(iii) AND (c)(ii)

CLAIMS:

(Amended) 3. The pharmaceutical composition according to [any of Claims] claim 1 [to 2], wherein the stabilizing agent is saccharose alone.

(Amended) 4. The pharmaceutical composition according to [any of claims] claim 1 [to 3], containing 3 or 10 mg/vial of hGRF.

(Amended) 5. The pharmaceutical composition according to [any of Claims] claim 1 [to 4] comprising 3 or 10 mg/vial of hGRF and 20.52 or 68.4 mg/vial of saccharose.

(Amended) 6. The pharmaceutical composition according to [any of Claims] claim 1 [to 5] further comprising buffering agents.

(Amended) 7. A process for preparing a pharmaceutical composition according to [any of Claims] claim 1 [to 6], comprising the preparation of an aqueous solution of the components, the distribution within containers and the lyophilization in the containers.

(Amended) 8. Forms of presentation of said pharmaceutical composition comprising the solid mixture according to [any of Claims] claim 1 [to 6], hermetically closed in a sterile condition within a container suited for storage before use and for reconstitution of the mixture into a solvent or into a solution for injectables.

(Amended) 9. A solution comprising the solid mixture according to [any of Claims] claim 1 [to 6], reconstituted in a solvent or a solution for injectables.

GRF-CONTAINING LYOPHILIZED PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

The present invention concerns Growth Hormone Releasing Factor (GRF) containing pharmaceutical compositions. More precisely, it concerns compositions of saccharose-stabilized GRF.

BACKGROUND OF THE INVENTION

In the early 1980's several groups isolated and characterized growth hormone releasing factor (GRF).

GRF (also called Somatorelin) is a peptide secreted by the hypothalamus, which acts on its receptor and can promote the release of growth hormone (GH) from the anterior pituitary. It exists as 44-, 40-, or 37-amino acid peptide; the 44-amino acid form may be converted physiologically into shorter forms. All three forms are reported to be active, the activity residing mainly in the first 29 amino acid residues. A synthetic peptide corresponding to the 1-29 amino acid sequence of human GRF [hGRF(1-29)], also called Sermorelin, has been prepared by recombinant DNA technology as described in European Patent EP 105 759.

Sermorelin has been used in the form of acetate for the diagnosis and treatment of growth hormone deficiency.

GRF has indeed a therapeutic value for the treatment of certain growth hormone related disorders. The use of GRF to stimulate the release of GH is a physiological method in promoting long bone growth or protein anabolism.

It is well known that the natural form of GRF can suffer from chemical degradation in aqueous solution, primarily of Asn at position 8, which results in reduced biological potency (Friedman, A.R. et al., *Int. J. Peptide. Protein Res.*, **37**, 14-20, 1991; Bongers, J., et al., *Int. J. Peptide. Protein Res.* **39**, 364-374, 1992).

The main hydrolytic reactions occurring in GRF are sensitive to pH and reported to be: rearrangement of Asp^3, at pH 4-6.5, cleavage of the Asp^3-Ala^4 bond at pH 2.5-4.5, deamidation and rearrangement of Asn^8 at pH above 7 (Felix A.M. et al., *Peptides*, editors: Giralt E. and Andreu D., pp 732-733, Escom Publishers 1991). Due to the combined degradation pathways, unstabilized aqueous solutions GRF are most stable in the pH range 4-5. Bongers et al. (Bongers et al., 1992) have shown that the deamidation reaction at Asn^8 increases rapidly as the pH is raised above pH 3.

WO 98/53844 describes stable liquid pharmaceutical compositions of hGRF containing nicotinamide and propylene glycol.

Various workers have made analogues of GRF by substitution of amino acids into the natural GRF sequence to improve the chemical stability (Serono Symposia USA, 1996; Friedman, 1991). While modification can be an effective means to improve the stability and retain bioactivity, it may be undesirable due to altered immunogenicity, which could be a problem for chronic therapies such as growth hormone deficiency.

According to EP 189 673 and US 4,963,529 (Sumitomo Pharma Inc.) GRF formulations can be prepared by lyophilization and stabilized by human serum albumin or glycine. JP 3083931 and EP 417 930 describe a GRF-containing nasal preparation which is rendered low-irritating to nasal mucosa by adding sodium chloride and/or sugar alcohols, such as mannitol or sorbitol thereto.

In order that materials like hGRF be provided to health care personnel and patients, these materials must be prepared as pharmaceutical compositions. Such compositions must maintain activity for appropriate periods of time, must be acceptable in their own right to easy and rapid administration to humans, and must be readily manufacturable. In many cases pharmaceutical formulations are provided in frozen or in lyophilized form. In this case, the composition must be thawed or reconstituted prior to use. The frozen or lyophilized form is often used to maintain biochemical integrity and the bioactivity of the medicinal agent contained in the compositions under a wide variety of storage conditions, as it is recognized by those skilled in the art that lyophilized preparations

often maintain activity better than their liquid counterparts. Such lyophilized preparations are reconstituted prior to use by the addition of suitable pharmaceutically acceptable diluent(s), such as sterile water for injection or sterile physiological saline solution, and the like.

Human GRF is found on the market in lyophilized formulations stabilized with mannitol GEREF®, Serono.

DESCRIPTION OF THE INVENTION

We have now found that saccharose confers a better stability to lyophilized formulations of hGRF.

The main object of the present invention is to provide pharmaceutical compositions comprising a solid intimate mixture of human GRF and a stabilizing amount of saccharose.

A further object is to provide a process for the preparation of said pharmaceutical composition, comprising the step of lyophilizing an aqueous solution of the components in the containers. Another object is to provide a presentation form of said pharmaceutical composition comprising the said solid mixture hermetically closed in a sterile condition within containers suitable for storage before use and suitable for reconstitution of the mixture for injectable substances. Such containers may be suitable for single dose administration or for multidose administration. Such lyophilized compositions also preferably contain a bacteriostatic agent. The bacteriostatic agent is preferably m-cresol.

The lyophilized compositions of the invention may further comprise buffering agents. Any buffer which is appropriate for pharmaceutical preparations may be used, for example acetate, phosphate or citrate. The amount of buffering agent to be added to the preparation will be such that the pH of the lyophilized compositions is kept within the desired range after reconstitution. The desired pH range according to this invention is between 2 and 7, preferably between 4 and 6.

Another object is to provide a solution of said solid mixture reconstituted into an injectable solution, such as water for injectable or physiological saline solution. Conveniently such reconstitution is carried out just before use for injection.

There is no critical limitation to the amount of saccahrose to be added to the active ingredient, but it will be appropriate to add from 1 to 200 mg/vial, preferably from 20 to 100 mg/vial of saccharose.

According to this invention the word "hGRF" is intended to cover any human GRF peptide, with particular reference to the 1-44, 1-40, 1-29 peptides and the corresponding amides thereof (containing $-NH_2$ at their end) or even a mixture thereof. They are all commercial compounds. The preferred hGRF is hGRF(1-29)-NH_2. There is no critical limitation to the amount of active ingredient present in each vial. Such amount is preferably comprised between 0.1 and 100 mg/vial.

The invention will now be described by means of the following Examples, which should not be construed as in any way limiting the present invention.

EXAMPLES

In order to evaluate the excipient's effect on the stability of the active ingredients, three formulations of recombinant hGRF have been prepared with various excipients: saccharose, mannitol and mannnitol/phosphate buffer. The filling volume was 2 ml. The compositions of the various formulations, which were prepared, are reported in Table 1.

Table 1

Formulation	hGRF (mg/ml)	Mannitol (mg/ml)	Saccharose (mg/ml)	Phosphoric Acid (mg/ml)	Sodium Hydroxide
1	5	18.2	-	-	-
2	5	18.2	-	0.98	q.s. to pH 4
3	5	-	34.2	-	-

The preparation of the lyophilizate was performed by dissolving the hGRF bulk powder in the solutions containing the stabilizers. The obtained solutions were filtered and filled into glass vials and lyophilized. The study of the stability of such formulations stored at 40°C and 50°C for 4 weeks, was performed by determinations of pH and peptide purity.

The chromatographic assay methodology (reverse phase HPLC) to evaluate the purity of hGRF was a gradient elution through a C-18 column, using a mobile phase (TFA/water/acetonitrile) at 1 ml/min and UV detection at 214 nm.

The pH was determined by a pHmeter on vials reconstituted with 5 ml of water for injection.

The results are summarized in Tables 2 and 3.

Table 2

Formulation	pH					
		40°C		50°C		
	T=0	3 weeks	4 weeks	2 weeks	3 weeks	4 weeks
1	6.8	7.4	7.4	7.2	7.3	7.4
2	4.8	5.2	5.4	5.6	5.4	5.7
3	5.5	5.4	5.5	5.4	5.4	5.4

Table 3

Formulation	Peptide Purity (%)					
		40°C		50°C		
	T=0	3 weeks	4 weeks	2 weeks	3 weeks	4 weeks
1	97.7	96.3	95.7	93.7	92.9	91.8
2	97.7	95.6	94.8	89.4	88.5	84.2
3	97.8	97.9	97.8	97.8	97.8	97.6

Results showed that the formulation containing saccharose presented a better stability profile when compared to the formulations containing mannitol or mannitol/phosphate buffer.

Additional formulations having the composition of formulation 3 described in Table 1 were manufactured in different containers (vials); the composition is reported in Table 4.

Table 4

Formulation	hGRF (mg/vial)	Saccharose (mg/vial)
3a	3	20.5
3b	10	68.4

The formulations were stored at 5°C, 25°C and 40°C and tested for stability using the analytical methods described before (pH, purity and titre by RP).

Stability data have been generated up to 24 weeks; the results are reported in Tables 5 to 7.

Table 5

Formulation	pH			
		5°C	25°C	40°C
	T=0	4 weeks	4 weeks	4 weeks
3a	4.95	5.03	5.02	5.12
3b	4.96	5.09	5.06	5.13

Table 6

Formulation 3a Storage Temperature = 40°C					
Test	**0 Time**	**4 weeks**	**8 weeks**	**12 weeks**	**24 weeks**
Purity (%)	97,8	97,8	97,3	97,0	96,0
Assay (mg/vial)	2,8	2,9	2,9	2,8	2,9
pH	4,95	5,12	5,25	5,30	5,43

Table 7

Formulation 3b Storage Temperature = 40°C					
Test	**0 Time**	**4 weeks**	**8 weeks**	**12 weeks**	**24 weeks**
Purity (%)	97,9	97,9	97,4	97,1	95,1
Assay (mg/vial)	9,8	9,8	10,0	9,8	8,8
pH	4,96	5,13	5,16	5,38	5,53

The stability of reconstituted solutions with 1.5 and 5 ml 0.3% m-cresol at 5±3 °C and 25±2°C up to 1 month was also studied.

The stability data on the reconstituted solutions are reported in Tables 8 to 10.

Table 8

Formulation	Storage (°C)	pH				
		T=0	1 week	2 weeks	3 weeks	4 weeks
3a	5°C	4.94	5.03	5.04	5.05	5.18
3b	5°C	4.96	5.07	5.04	5.14	5.25
3a	25°C	4.94	5.05	5.07	5.07	5.19
3b	25°C	4.96	5.14	5.12	5.14	5.24

Table 9

Formulation	Storage (°C)	Peptide Purity (%)				
		T=0	1 week	2 weeks	3 weeks	4 weeks
3a	5°C	97.6	97.6	97.5	97.6	97.4
3b	5°C	97.6	97.5	97.4	97.5	97.4
3a	25°C	97.6	96.4	95.4	94.5	93.5
3b	25°C	97.6	96.3	95.4	94.7	93.5

Table 10

Formulation	Storage (°C)	Peptide Content (mg/vial)				
		T=0	1 week	2 weeks	3 weeks	4 weeks
3a	5°C	2.9	3.0	2.5	3.0	2.9
3b	5°C	9.6	10.0	9.1	10.0	9.9
3a	25°C	2.9	2.9	2.8	2.8	2.8
3b	25°C	9.6	10.0	9.3	9.5	9.4

EXAMPLE OF PHARMACEUTICAL MANUFACTURING

Materials: extra pure saccharose DAB, Ph Eur, BP, NF (Merck); water for injectables.

As containers have been used vials DIN 2R and DIN 6R (borosilicate glass type I), rubber closures (Pharmagummi W1816 V50) and aluminum rings and flip-off caps (Pharma-Metal GmbH).

Preparation of hGRF solution containing saccharose: (for 200 vials containing each 3 or 10 mg hGRF).

Saccharose (17.1g) are dissolved into water for injectables (500 ml) in order to obtain the starting saccharose solution.

The bulk of the hGRF 2 g) is added to the saccharose solution so as to obtain a final weight of 400 g the solution is filtered through a 0,22 µm Durapore sterile filter (Millipore).

Filling up and lyophilization

The vials are filled up with 0.6 and 2 ml of hGRF sterile solution , transferred to the freeze-dryer and lyophilized according to the following cycle:

- freezing: -25°C for 3 hrs
  -15°C for 1 hr
  -45°C for 3 hrs
- primary drying: -10°C for 13 hrs
- secondary drying: from –10°C to +40°C in 8 hrs; +40°C till end of cycle

CLAIMS

1. A pharmaceutical composition comprising a solid intimate mixture of human growth releasing factor (GRF) and a stabilizing amount of saccharose, alone or in combination with other excipients.

2. The pharmaceutical composition according to Claim 1, wherein the solid intimate mixture is a lyophilizate.

3. The pharmaceutical composition according to any of Claims 1 to 2, wherein the stabilizing agent is saccharose alone.

4. The pharmaceutical composition according to any of claims 1 to 3, containing 3 or 10 mg/vial of hGRF.

5. The pharmaceutical composition according to any of Claims 1 to 4 comprising 3 or 10 mg/vial of hGRF and 20.52 or 68.4 mg/vial of saccharose.

6. The pharmaceutical composition according to any of Claims 1 to 5 further comprising buffering agents.

7. A process for preparing a pharmaceutical composition according to any of Claims 1 to 6, comprising the preparation of an aqueous solution of the components, the distribution within containers and the lyophilization in the containers.

8. Forms of presentation of said pharmaceutical composition comprising the solid mixture according to any of Claims 1 to 6, hermetically closed in a sterile condition within a container suited for storage before use and for reconstitution of the mixture into a solvent or into a solution for injectables.

9. A solution comprising the solid mixture according to any of Claims 1 to 6, reconstituted in a solvent or a solution for injectables.

10. The solution according to any of Claim 9, wherein the pH in comprised between 4 and 6.

UNITED STATES OF AMERICA COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION	FILE NO. I0717.0002

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

GRF-CONTAINING LYOPHILIZED PHARMACEUTICAL COMPOSITIONS

the specification of which is attached hereto, unless the following box is checked:

: was filed on 29 June 2000 as United States patent Application Number or PCT International patent application number PCT/EP00/06061 and was amended on _____ (if any).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information known to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code §119 of any foreign application(s) for patent or inventor's certificate or United States provisional application(s) listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign or Provisional Application(s)

COUNTRY	APPLICATION NUMBER	DATE OF FILING *(day, month, year)*	PRIORITY CLAIMED UNDER 35 U.S.C. § 119
Europe	99112421.5	30 June 1999	YES XX NO
			YES ___ NO
			YES ___ NO

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

UNITED STATES APPLICATION NUMBER	DATE OF FILING *(day, month, year)*	STATUS *(patented, pending, abandoned)*

I hereby appoint customer no. _____ DICKSTEIN, SHAPIRO, MORIN & OSHINSKY, LLP, and the members of the firm, Edward A. Meilman, Reg. No. 24,735, Gary M. Hoffman, Reg. No. 26,411, Steven I. Weisburd, Reg. No. 27,409, Thomas J. D'Amico, Reg. No. 28,371, Donald A. Gregory, Reg. No. 28,954, Stephen A. Soffen, Reg. No. 31,063, James W. Brady, Jr., Reg. No. 32,115, Jon D. Grossman, Reg. No. 32,699, Mark J. Thronson, Reg No. 33,082, Michael J. Scheer, Reg. No. 34,425, and Eric Oliver, Reg. No. 35,307, as attorneys with full power of substitution and revocation to prosecute this application, to transact all business in the Patent & Trademark Office connected therewith and to receive all correspondence.

SEND CORRESPONDENCE TO: DICKSTEIN, SHAPIRO, MORIN & OSHINSKY, LLP
1177 Avenue of the Americas, 41st Floor
New York, NY 10036-2714

DIRECT TELEPHONE CALLS TO:
(212) 835-1400

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FULL NAME OF SOLE OR FIRST INVENTOR	INVENTOR'S SIGNATURE	DATE
Fabrizio SAMARITANI	x [signature]	x 14-Mar-2002
RESIDENCE *(City and either State or Foreign Country)*		COUNTRY OF CITIZENSHIP
Roma, Italy ITY		Italy
POST OFFICE ADDRESS		
Via Luigi Chiala, 130, I-00139, Roma, Italy		
FULL NAME OF SECOND JOINT INVENTOR (IF ANY)	INVENTOR'S SIGNATURE	DATE
Alessandra DEL RIO	x [signature]	14/MAR/2002
RESIDENCE *(City and either State or Foreign Country)*		COUNTRY OF CITIZENSHIP
Roma, Italy ITY		Italy
POST OFFICE ADDRESS		
Viale Romualdo Chiesa, 15, I-00144, Roma, Italy		